CLAIMS:

1. A variant of an isolated DNA virus which replicates *via* an RNA intermediate wherein said variant comprises a nucleotide mutation in a gene encoding a DNA polymerase or part thereof resulting in at least one amino acid addition, substitution and/or deletion to said DNA polymerase.

2. A variant of an isolated DNA virus which replicates *via* a RNA intermediate wherein said variant comprises a nucleotide mutation in a gene encoding a surface component or a part thereof resulting in at least one amino acid addition, substitution and/or deletion to said surface component.

3. A variant of an isolated DNA virus which replicates *via* an RNA intermediate at least wherein said variant comprises a nucleotide mutation in an overlapping portion of at least two open reading frames resulting in an amino acid addition, substitution and/or deletion to translation products of said two open reading frames.

4. A variant according to claim 1 or 2 or 3 wherein said DNA virus is hepatitis B virus (HBV).

5. A variant according to claim 1 or 3 wherein the amino acid mutation is in the B domain and/or C domain of the HBV DNA polymerase.

6. A variant according to claim 2 or 3 wherein the amino acid mutation corresponds to the B domain and/or C domain of the HBV DNA polymerase.

7. A variant according to claim 1 or 3 comprising a mutation in one or more of amino acids within the sequence (SEQ ID NO:25)

Q/K T Y/F G R/W KLHL Y/L S/A HPI I/V LGFRK I/L PMG V/G GLS PFLL

AQFTSAI C/L S

of HBV DNA polymerase.

8. A variant according to claim 7 comprising a mutation in one or more amino acids within the sequence:

S/A HPI I/V LGFRK I/L PMG V/G GLSPFLLAQFTSAIC/L S

of HBV DNA polymerase.

9. A variant according to claim 1 or 3 comprising a nucleotide sequence which encodes a DNA polymerase having the amino acid sequence:

$X_1HPIX_2LGX_3RKX_4PMGX_5GLSX_6FLX_7AQFTSAX_8X_9$.....
$X_{10}FX_{11}YX_{12}DDX_{13}VLGAX_{14}X_{15}$

wherein X_1 is S or A;
X_2 is I or V;
X_3 is F or L;
X_4 is I or L;
X_5 is L or V or G;
X_6 is P or L;
X_7 is L or M;
X_8 is I or L;
X_9 is C or L;
X_{10} is A or V;
X_{11} is S or A;
X_{12} is M or I or V;
X_{13} is V or L or M;
X_{14} is K or R; and/or
X_{15} S or T;

and wherein said variant exhibits reduced sensitivity to a nucleoside sensitivity to a nucleoside

analogue, such as famciclovir (penciclovir) and/or lamivudine (3TC).

10. A variant according to claim 2 or 3 having a mutation in one or more of amino acids 118 to 169 or 169 to 207 of HBV surface antigen.

11. A variant according to claim 10 comprising a DNA polymerase having the amino acid sequence: (SEQ ID NO: 42 and SEQ ID NO: 43)

$X_{16}TX_{17}X_{18}X_{19}KLHLX_{20}X_{21}HPX_{22}LGX_3RKX_4PMGX_5GLSX_6FLX_7AQFTSAX_8X_9$ .....
$X_{10}FX_{11}YM_{12}DDX_{13}VLGAX_{14}X_{15}$

wherein:
X_{16} is Q or K;
X_{17} is Y or F;
X_{18} is G ~~or E~~;
X_{19} is R or ~~W or K~~;
X_{20} is Y or L;
X_{21} is S or A;
X_{22} is I or V;
X_3 is F or L;
X_4 is I or L;
X_5 is L or V or G;
X_6 is P or L;
X_7 is L or M;
X_8 is I or L;
X_9 is C or L;
X_{10} is A or V;
X_{11} is S or A;
X_{12} is M or I or V;
X_{13} is V or L or M;
X_{14} is K or R; and/or
X_{15} S or T;

and wherein said variant exhibits reduced sensitivity to a nucleoside sensitivity to a nucleoside analogue, such as famciclovir (penciclovir) and/or lamivudine (3TC).

12. A variant according to claim 1 or 2 or 3 selected from Ile509Val, Phe512Leu, Val519Leu, Pro523Leu, Leu526Met, Ile533Leu, Met550Val/Ile, Ser559Thr, ~~Gly498Glu~~, Arg/Trp499~~Lys~~Glu, Thr530Ser.

13. An HBV variant comprising a mutation in the nucleotide sequence encoding a DNA polymerase resulting in an amino acid addition, substitution and/or deletion in said DNA polymerase in its B domain and/or C domain or in a region proximal thereto, provided said mutation is not in the YMDD motif of the C domain alone, and wherein said variant exhibits decreased sensitivity to a nucleoside analogue.

14. An HBV variant comprising a mutation in the nucleotide sequence encoding a viral surface component resulting in an amino acid addition, substitution and/or deletion in said viral surface component in a region corresponding to the B domain and/or C domain of HBV DNA polymerase or a region proximal to the B domain and/or C domain of HBV DNA polymerase and wherein said variant exhibits decreased interactivity of immunological reagents to said viral surface component.

15. An HBV variant comprising a mutation in the nucleotide sequence encoding a viral surface component resulting in an amino acid addition, substitution and/or addition in said viral surface component in a region defined by amino acids 118 to 169 and/or 169 to 207 of the HBV surface antigen or functionally equivalent region wherein said variant exhibits decreased interactivity of immunological reagents to said viral surface component.

16. An HBV variant comprising a mutation in an overlapping open reading frame in its genome wherein said mutation is in the B and/or C domain of DNA polymerase provided that it is not in the YMDD motif of the C domain alone; and in the overlapping region corresponding to amino acids 118 to 169 and/or 169 to 207 or equivalent of HBV surface antigen and wherein

said variant exhibits decreased sensitivity to a nucleotide analogue and exhibits decreased interactivity to immunological reagents specific to HBV surface antigens.

17. Accordingly, the present invention is directed to an HBV having the nucleotide sequence as set forth in SEQ ID NO:17 or a derivative thereof having a single or multiple nucleotide addition, substitution and/or deletion thereto such as a nucleotide sequence having at least 60% similarity to SEQ ID NO:17.

18. A variant HBV exhibiting reduced sensitivity to a nucleoside analogue and reduced interactivity to an antibody to wild-type HBV surface antigen, said HBV variant characterised by one or more of the following characteristics:

(i) a nucleotide sequence of its genome as set forth in SEQ ID NO:17 or a sequence having at least 60% similarity thereto;

(ii) a nucleotide sequence capable of hybridising to SEQ ID NO:17 under low stringency conditions at 42°C;

(iii) a mutation in an overlapping portion of open reading frames for DNA polymerization and HBV surface antigen; and

(iv) a mutation in the B and/or C domain of HBV DNA polymerase and is a region corresponding to amino acids 118 to 169 and/or 169 to 207 of HBV surface antigen.

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19. A method for ~~a method for~~ determining the potential for an HBV to exhibit reduced sensitivity to a nucleoside analogue, said method comprising isolating DNA or corresponding mRNA from said HBV and screening for a mutation in the nucleotide sequence encoding HBV DNA polymerase resulting in at least one amino acid substitution, deletion and/or addition in the B domain or C domain or a region proximal thereto of said DNA polymerase wherein the presence of such a mutation is an indication of the likelihood of resistance to said nucleoside analogue.

20. A method for determining the potential for an HBV to exhibit reduced interactivity to antibody to HBV surface antigen, said method comprising isolating DNA or corresponding

mRNA from said HBV and screening for a mutation in the nucleotide sequence encoding HBV surface antigen resulting in at least one amino acid substitution, deletion and/or addition in amino acids 118 to 169 and/or 169 to 207 of said surface antigen or a region proximal thereto of said surface antigen wherein the presence of such a mutation is an indication of the likelihood of reducing interactivity of said antibodies to said mutated surface antigen.

21. A method according to claim 19 or 20 wherein the assay detects a mutation selected from Ile509Val, Phe512Leu, Val519Leu, Pro523Leu, Leu526met, Ile533Leu, Met550Val/Ile, ~~Ser559Thr, Gly498Glu~~ Arg/Trp499~~Lys, Thr530Ser.~~ Glu

22. A method for determining whether an HBV isolate encodes a variant DNA polymerase, said method comprising determining the amino acid sequence of its DNA polymerase directly or *via* a nucleotide sequence and comparing same to the amino acid sequence below: (SEQ ID NO:29)

DOMAIN A

421 430 440 450

$S^{N}_{D}LSWLSLD\ VSAAFYH^{I}_{P}PL\ HPAAMPHLL^{I}_{V}\ GSSGL^{S}_{D}RYVA$

460 470 480 490

$RLSS^{T}_{N}S^{R}_{N}N^{N}_{I}{}^{*}N\ N^{Y}_{H}Q^{H}_{Y}G_{R}{}^{***}D_{N}LH\ D^{N}_{N}S^{S}_{Y}CSR^{N}_{Q}LYVS\ L^{L}_{M}LLY^{K}_{Q}T^{Y}_{F}G^{R}_{R}W$

DOMAIN B

500 510 520 530

$KLHL^{Y}_{L}S_{A}HPI^{I}_{V}\ LGFRK^{I}_{L}PMG^{V}_{G}\ GLSPFLLAQF\ TSAI^{C}_{L}A_{S}V_{M}{}^{V}_{T}R_{C}R$

DOMAIN C

540 550 560

$AF^{F}_{P}HC^{L}_{V}{}^{A}_{V}F^{S}_{A}Y\ MDD^{V}_{L}{}_{M}VLGA^{K}_{R}S_{T}\ V_{G}Q_{E}H^{L}_{S}R^{E}_{S}F^{L}_{F}Y^{T}_{A}A_{S}$

DOMAIN D DOMAIN E

570 580 590 600

$V_{I}T_{C}N_{S}F_{V}LLS_{D}L_{V}GI\ HLNP^{N}_{Q}KTKRW\ GYSLNFMGY^{V}_{I}I\ G$

where the presence of a different amino acid from the consensus sequence indicates a putative HBV variant.

add D2 add E1 add G47 add H47